

REMARKS**Amendments to the Claims**

Claims 1-17, 31-43, 54-61, 63, 67-73 93-101, 114-121 and 123-133 are pending. The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1, 12, 31, 32, 36-43, 48, 54, 55, 58-61, 93, 94, 114, 115, 118-121, 123, 125 and 126 were amended; Claims 62, 64-66, 80, 84-92, 95, 98 and 122 were canceled; Claims 48-53 were withdrawn; and Claims 134 and 135 are new. The Applicants state that all amended claims do not add new subject matter to the present specification.

Support for Claims 1, 12 and 48 can be found throughout the specification, such as, e.g., ¶¶ 57, 79, 132-134; and Example IX.

Support for Claim 31 can be found throughout the specification, such as, e.g., ¶¶ 105, 108 and 111.

Support for Claim 54, 55, 58-61 can be found throughout the specification, such as, e.g., ¶¶ 83-87.

Support for Claims 93, 94, 134 and 135 can be found throughout the specification, such as, e.g., ¶¶ 58-62.

Support for Claims 123, 125 and 126 can be found throughout the specification, such as, e.g., ¶¶ 58-62 and 115-120.

Restriction Requirement

The Examiner has restricted Claims 48-53 as allegedly claiming a non-elected invention under 37 C.F.R. § 1.143(b) because the claimed method was deemed an independent and distinct invention. While withdrawing Claims 48-53, the Applicants respectfully traverse this restriction requirement pursuant to 37 C.F.R. § 1.143.

According to 37 C.F.R. § 1.145, if, after an office action on an application, the applicant presents claims directed to an invention distinct from and independent of the invention previously claimed, the applicant will be required to restrict the claims to the invention previously claimed if the amendment is entered.

The Applicants respectfully submit that the method claimed in Claims 48-53 are not directed to an independent and distinct method because these claims are directed towards aspects of the elected method presently claimed in Claims 1-16, 55-61, 63 and 67-73.

First, Claims 1-16, Claims 48-53 and Claims 54-61, 63 and 67-73 are all directed, in part, toward a method of predicting or determining immunoresistance to botulinum toxin therapy in an individual where the presence of antibodies immunoreactive with specific BoNT/A peptides indicates immunoresistance to a botulinum toxin therapy. Immunoreactivity is determined by the level of antibodies immunoreactive with at least one BoNT/A peptide. For Claims 1-16, the BoNT/A peptides that may be used consist of amino acids 785-803 of SEQ ID NO: 1, amino acids 981-999 of SEQ ID NO: 1, amino acids 1051-1069 of SEQ ID NO: 1, amino acids 1121-1139 of SEQ ID NO: 1, amino acids 1275-1296 of SEQ ID NO: 1, a conservative BoNT/A amino acid sequence variant thereof and an immunoreactive BoNT/A amino acid sequence fragment thereof. For Claims 48-53 and Claims 54-61, 63 and 67-73, the BoNT/A peptides that may be used have a length of at most 60 amino acids and comprise an amino acid sequence selected from the group consisting of amino acids 785-803 of SEQ ID NO: 1, amino acids 981-999 of SEQ ID NO: 1, amino acids 1051-1069 of SEQ ID NO: 1, amino acids 1121-1139 of SEQ ID NO: 1, amino acids 1275-1296 of SEQ ID NO: 1, a conservative BoNT/A amino acid sequence variant thereof and an immunoreactive BoNT/A amino acid sequence fragment thereof. In all claims, the antibodies immunoreact with amino acids 785-803 of SEQ ID NO: 1, amino acids 981-999 of SEQ ID NO: 1, amino acids 1051-1069 of SEQ ID NO: 1, amino acids 1121-1139 of SEQ ID NO: 1, amino acids 1275-1296 of SEQ ID NO: 1, a conservative BoNT/A amino acid sequence variant thereof and an immunoreactive BoNT/A amino acid sequence fragment thereof.

Second, Claims 1-16, Claims 48-53 and Claims 54-61, 63 and 67-73 are all directed, in part, toward determining the presence or absence of antibodies immunoreactive with the recited specific BoNT/A peptides. Claims 1-16 determine the amount of total neutralizing anti-BoNT/A antibodies, with dependent Claim 14 determining the amount of the IgG component of neutralizing anti-BoNT/A antibodies. Claims 54-61, 63 and 67-73 determine the amount of total neutralizing anti-BoNT/A antibodies. Claims 48-53 determine the amount of the IgG component of neutralizing anti-BoNT/A antibodies.

Thus, the method claimed by Claims 1-16, Claims 48-53 and Claims 54-61, 63 and 67-73 are directed toward different aspects of a method of predicting or determining immunoresistance to botulinum toxin therapy in an individual. Claims 1-16 determine the presence of total neutralizing anti-BoNT/A antibodies (or the IgG component) using specific BoNT/A peptides having a length of 19 or 22 amino acids. Claims 54-61, 63 and 67-73 determine the presence of total neutralizing anti-BoNT/A antibodies using specific BoNT/A peptides having a length of at most 60 amino acids. Claims 48-53 determine the presence of the IgG component from total neutralizing anti-BoNT/A antibodies using specific BoNT/A peptides having a length of at most 60 amino acids.

For these reasons, the Applicant's respectfully submit that the method of Claims 48-53 is directed toward aspects of a previously claimed invention and not to an independent and distinct invention. Therefore, the Applicants respectfully request withdrawal of the restriction requirement for Claims 48-63 because the restriction was improper pursuant to 37 C.F.R. § 1.142(b).

Rejection Pursuant to 35 U.S.C. §102(b)

I. Dertzbaugh Reference

The Examiner has rejected Claims 1-13, 15, 17, 31-43, 54-61, 114-121 and 123-132 as allegedly anticipated under 35 U.S.C. §102(b) by Mark T. Dertzbaugh and Michael W. West, *Mapping of protective and Cross-reactive domains of the Type A Neurotoxin of Clostridium botulinum*, 14(16) Vaccine 1538-1544 (1996), hereafter the Dertzbaugh reference. Specifically, the Examiner contends that the claimed BoNT/A peptides are not limited to an

amino acid length of no more than 60 amino acids. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

According to *MPEP* § 2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

Currently amended Claims 1-13, 15 and 17 are directed towards BoNT/A peptides limited to a length of 19 amino acids. Claims 31-43, 48-61, 114-121 are directed towards BoNT/A peptides limited to a length of no more than 60 amino acids. Claims 123-132 are directed towards BoNT/A peptides limited to a length of no more than 30 amino acids. Thus, the Dertzbaugh reference does not anticipate the amended claims because this reference discloses 10 BoNT/A polypeptides that range from 125-209 amino acids in length, see, e.g., p. 1540, Figure 1. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1-13, 15, 17, 31-43, 54-61, 114-121 and 123-132.

II. Atassi Reference

The Examiner has rejected Claims 93-94, 96 and 98 as allegedly anticipated under 35 U.S.C. §102(b) by M. Zouhair Atassi, *Immune Recognition and Cross-Reactivity of Botulinum Neurotoxins*, pp. 385-407: in *Scientific and Therapeutic Aspects of Botulinum Toxin* (eds. Mitchell F. Brin et al., 2002), hereafter the Atassi reference. Specifically, the Examiner contends that that this reference discloses a BoNT/A peptide having a length of no more than 30 amino acids and comprising amino acids 659-677 of SEQ ID NO: 1. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

Currently amended Claims 93-94, 96 and 98 do not recite the phrase “amino acids 659-677 of SEQ ID NO: 1.” Thus, the Atassi reference does not anticipate the amended claims because this reference does not teach a BoNT/A peptide comprising the amino acids 659-677 of SEQ ID NO: 1. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93-94, 96 and 98.

III. Oblatt-Montal Reference

The Examiner has rejected Claims 93-94, 96 and 98 as allegedly anticipated under 35 U.S.C. §102(b) by Myrta Oblatt-Montal et al., *Formation of Ion Channels in Lipid Bilayers by a Peptide with the Predicted Transmembrane Sequence of Botulinum Neurotoxin A*, 4 Protein Sci. 1490-1497 (1995), hereafter the Oblatt-Montal reference. Specifically, the Examiner contends that that this reference discloses a BoNT/A peptide having a length of no more than 30 amino acids and comprising amino acids 659-677 of SEQ ID NO: 1. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

Currently amended Claims 93-94, 96 and 98 do not recite the phrase "amino acids 659-677 of SEQ ID NO: 1." Thus, the Oblatt-Montal reference does not anticipate the amended claims because this reference does not teach a BoNT/A peptide comprising the amino acids 659-677 of SEQ ID NO: 1. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93-94, 96 and 98.

IV. Sesardic Publication

The Examiner has rejected Claim 93 and 96 as allegedly anticipated under 35 U.S.C. §102(b) by Dorothea Sesardic et al., *Botulinum Toxin Polypeptides and Their Use as Vaccine Enhancing Agents*, International Patent Application Publication WO 94/21684 (Sep. 29, 1994), hereafter the Sesardic reference. Specifically, the Examiner contends that that this reference discloses a BoNT/A peptide having a length of no more than 30 amino acids and comprising amino acids 827-845 of SEQ ID NO: 1. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

Currently amended Claims 93 and 96 do not recite the phrase "amino acids 827-845 of SEQ ID NO: 1." Thus, the Sesardic reference does not anticipate the amended claims because this reference does not teach a BoNT/A peptide comprising the amino acids 827-845 of SEQ ID NO: 1. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93 and 96.

V. Raju Publication

The Examiner has rejected Claims 93 as allegedly anticipated under 35 U.S.C. §102(b) by Raghavanpillai Raju et al., *Epitope Repertoire of Human CD4+ Lines Propagated with Tetanus Toxoid or with Synthetic Tetanus Toxin Sequences*, 9 J. Autoimmunity 79-88 (1996), hereafter the Raju reference. Specifically, the Examiner contends that that this reference discloses a BoNT/A peptide having a length of no more than 30 amino acids and comprising amino acids 634-642 of SEQ ID NO: 1. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

According to *MPEP* § 2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

Claim 93 is directed, in part, toward a BoNT/A peptide of SEQ ID NO: 1 having a length of at most 30 amino acids and comprising amino acids 631-649 or a conservative BoNT/A amino acid sequence variant comprising 1-4 conservative amino acid substitutions to amino acids 631-649 of SEQ ID NO: 1.

The Raju reference discloses the TeNT peptide IDKISDVSTIVPYIGPALNI. Amended Claim 93 is directed, in part, towards a BoNT/A peptide having a length of 30 amino acids and comprising amino acids 631-649 of SEQ ID NO: 1, indicating that this BoNT/A peptide must have the amino acid sequence TIIPYIGPALNIGNMLYK. Alignment of these two peptides reveals nine amino acid changes in the TeNT H176-195 relative to BoNT/A amino acids 631-649 of SEQ ID NO: 1 (asterisks residues):

TeNT H176-195	IDKISDVSTIVPYIGPALNI
	: : : : : : : :
BoNT/A 631-649	TIIPYIGPALNIGNMLYK
	* * * * *

Thus, the Raju reference does not anticipate the amended claim because this reference does not teach a BoNT/A peptide comprising TIIPYIGPALNIGNMLYK or a conservative variant comprising 1-4 conservative amino acid substitutions to amino acids 631-649 of SEQ ID NO: 1. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93.

Rejection Pursuant to 35 U.S.C. §103, Obviousness

The Examiner has rejected Claims 1-16, 55-61, 63, 67-73, 93, 94, 96-101, 104-112, 123-133 as allegedly being obvious under 35 U.S.C. § 103(a) over Mark T. Dertzbaugh and Michael W. West, *Mapping of protective and Cross-reactive domains of the Type A Neurotoxin of Clostridium botulinum*, 14(16) Vaccine 1538-1544 (1996), hereafter "the Dertzbaugh reference," in view of Sina Bavari et al., *Antibodies Against Type A Botulinum Neurotoxin*, U.S. Patent Publication 2004/0110284 (Jun. 10, 2004), hereafter "the Bavari publication."

Specifically, the Examiner contends that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the peptides disclosed in the Dertzbaugh reference to lengths of less than 60 or 40 amino acids as taught by the Bavari publication because both references are directed to identifying protective epitopes presented by *Clostridium botulinum* for vaccine development and the Bavari publication teaches the advantage of peptide immunogens of about 25 amino acids in length for determining the presence or induction of neutralizing antibodies because the peptides can be recombinantly expressed. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

I. Claims 1-16

Claims 1-16 are directed, in part, toward a method of predicting or determining immunoresponse to botulinum toxin therapy in an individual where the presence of antibodies immunoreactive with specific BoNT/A peptides indicates immunoresponse to a botulinum toxin therapy. The present specification defines immunoresponse to botulinum toxin therapy as a reduction in a beneficial effect of botulinum toxin therapy in an individual resulting from the presence in the individual of antibodies that bind to botulinum toxin, thereby inactivating the toxin, see, e.g., ¶ 6; and ¶ 83. It is well known in the art that anti-BoNT/A antibodies that inactivate BoNT/A are termed neutralizing anti-BoNT/A antibodies, whereas, anti-BoNT/A antibodies that do not inactivate BoNT/A are termed non-neutralizing anti-BoNT/A antibodies. One of the BoNT/A peptides used to detect neutralizing anti-BoNT/A antibodies in Claims 1-16 consists of amino acids 785-803 of SEQ ID NO: 1, a

conservative variant thereof or an immunoreactive fragment thereof, see, e.g., ¶ 58; and ¶ 132. Claims 1-11 also require at least one additional BoNT/A peptide to practice this method, where the additional BoNT/A peptide that detects neutralizing anti-BoNT/A antibodies consists amino acids 981-999 of SEQ ID NO: 1, amino acids 1051-1069 of SEQ ID NO: 1, amino acids 1121-1139 of SEQ ID NO: 1 or amino acids 1275-1296 of SEQ ID NO: 1 a conservative variant or an immunoreactive fragment thereof, see, e.g., ¶ 58; and ¶ 132.

Dertzbaugh and Bavari teach away from the claimed method

According to MPEP § 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The Applicants respectfully submit that it would not be obvious to combine the cited references because the both the Dertzbaugh reference and the Bavari publication teach away from a method of determining immunoresistance to botulinum toxin therapy using a BoNT/A peptide consists of amino acids 785-803 of SEQ ID NO: 1 a conservative variant thereof or an immunoreactive fragment thereof as presently claimed in Claims 1-16.

The Dertzbaugh reference discloses 10 BoNT/A polypeptides that range from 125-209 amino acids in length, see, e.g., p. 1540, Figure 1. This reference teaches away from the presently claimed method on two accounts.

First, the Dertzbaugh reference discloses that BoNT/A epitopes appear to be conformationally-sensitive indicating that the use of "synthetic peptides to map the location of these epitopes may be unproductive due to their lack of tertiary structure." See pg. 1538, col. 2, ¶ 2, lines 18-22. Based on this disclose, the Dertzbaugh reference teaches that a BoNT/A fragment must be long enough to maintain tertiary structure, and therefore be immunogenic, but small enough to identify the general location of the epitope, see, e.g., pg. 1538, col. 2, ¶ 3, line 1 through pg. 1539, col. 1, ¶ 1, line 5; pg. 1541 col. 2, ¶ 2, lines 7-10. The solution disclosed in the Dertzbaugh reference was the use of overlapping BoNT/A fragments 125-209 amino acids in length to map BoNT/A epitopes, see, e.g., p. 1540, Figure 1. Thus, the Dertzbaugh reference teaches away from the use of BoNT/A peptides consisting of 19 amino acids because, according to the teachings of this reference, such peptides would not work because they do not maintain the tertiary structure required to elicit

an immune response. Therefore, a person of ordinary skill in the art would not use a BoNT/A peptide of 19 or 22 amino acids in length in a method of predicting or determining immunoresistance to botulinum toxin therapy as presently claimed in Claims 1-16 because, according to the Dertzbaugh reference, this BoNT/A peptide would not maintain the tertiary structure required to recognize anti-BoNT/A antibodies. As all BoNT/A peptides recited in Claims 1-16 are either 19 amino acids or 22 amino acids in length, the Dertzbaugh reference teaches away for the presently claimed method.

Second, the Dertzbaugh reference teaches away from the use of the BoNT/A peptide consisting of amino acids 785-803 of SEQ ID NO: 1 a conservative variant thereof or an immunoreactive fragment thereof. The Dertzbaugh reference identified two regions of BoNT/A that elicit protective immunity, these regions consisting of amino acids 455-661 and amino acids 1150-1289, see, *e.g.*, pg. 1541, col. 2, ¶ 1, lines 8-23; pg. 1543, col. 1, ¶ 4, lines 1-5; Table 1. Further, the Dertzbaugh reference stresses the importance of these two BoNT/A fragments by stating that "[f]uture efforts can now be directed towards studying the regions of BoNT that include these fragments." See, pg. 1543, col. 2, ¶ 4, lines 7-9. In fact, according to the Dertzbaugh reference, the BoNT/A fragment containing amino acids 785-803 elicited no protective immunity, see Table 1, BoNT/A fragment 630-808. The inability of BoNT/A fragment 630-808 to provide any protection against anti-BoNT/A antibodies would indicate to a person of ordinary skill in the art that antibodies produced by this fragment would not inactivate BoNT/A after binding to the toxin, *i.e.*, anti-BoNT/A antibodies produced from BoNT/A fragment 630-808 are non-neutralizing antibodies. Non-neutralizing anti-BoNT/A antibodies do not cause immunoresistance to a botulinum toxin therapy in an individual. Thus, the Dertzbaugh reference teaches that amino acids 785-803 from BoNT/A would not work for detecting anti-BoNT/A antibodies that cause immunoresistance to a botulinum toxin therapy because BoNT/A fragment 630-808 did not elicit protective immunity. Therefore, a person of ordinary skill in the art would not use a BoNT/A peptide consisting of amino acids 785-803 in a method of predicting or determining immunoresistance to botulinum toxin therapy as presently claimed in Claims 1-16 because, according to the Dertzbaugh reference, this BoNT/A peptide would not recognize anti-BoNT/A antibodies that cause immunoresistance. As a BoNT/A peptide consisting of amino acids 785-803 of SEQ ID NO: 1 is an element recited in Claims 1-16, the Dertzbaugh reference teaches away for the presently claimed method.

The teachings of the Bavari publication cannot make up for the deficient teachings of the Dertzbaugh reference because this patent not only fails to provide any teaching contrary to the Dertzbaugh reference, its disclosure also teaches away from the presently claimed method.

First, the Applicant's respectfully disagree with the characterization of the teaching disclosed Bavari publication as "means and methods of producing overlapping peptide of 25 amino acids in length for epitope mapping botulinum toxins." See, May 18, 2006 Office Action, pg.8, item 15, ¶ 2, lines 1-2. The Bavari publication only disclosed three non-overlapping BoNT/A peptides consisting of amino acids 449-473, 1157-1181 and 1230-1253. Furthermore, the Bavari publication does not "teach the advantage of shorter, more readily expressed peptide immunogens that about 25 amino acids in length as they are readily used for determining the presence of or the induction of neutralizing polyclonal and/or monoclonal antibodies because the peptides can be expressed recombinantly." See, May 18, 2006 Office Action, pg.9, item 15, ¶ 2, lines 5-8. The Bavari publication teaches the use of large BoNT/A fragments to generate antibodies and only after determining whether such antibodies were neutralizing were synthetic BoNT/A peptides used to further map antigenic epitopes, see, e.g., ¶¶ 30-31; Examples 1-3. The three BoNT/A peptide fragments cited by the Examiner were used only in follow-on confirmation experiments for the findings obtained from BoNT/A fragments of approximately 140 to 160 amino acids in length, see ¶ 59, lines 4-8; and ¶ 91, lines 1-4.

Second, in generating neutralizing antibodies against BoNT/A, the Bavari publication teaches that such antibodies "might be best generated if one immunizes animals with BoNT/A H_c, the protective, non-toxic receptor binding domain of BoNT/A." See ¶ 85, lines 1-4. Thus, the Bavari publication teaches that the use of a BoNT/A peptide derived from the H_N domain (translocation domain) is not desirable for the production of neutralizing anti-BoNT/A antibodies. The amino acids 785-803 of SEQ ID NO: 1 lie within the H_N domain of BoNT/A. Thus, a person of ordinary skill in the art would not use a BoNT/A peptide derived from the H_N domain in a method of predicting or determining immuno-resistance to botulinum toxin therapy as presently claimed in Claims 1-16 because, according to the Bavari publication, this BoNT/A peptide would not recognized anti-BoNT/A antibodies that cause

immunoresistance. As a BoNT/A peptide consisting of amino acids 785-803 of SEQ ID NO: 1 is an element recited in Claims 1-16, the Bavari publication teaches away for the presently claimed method.

Third, in generating neutralizing antibodies against BoNT/A, it appears that the Bavari publication used the five BoNT/A fragments domain generated by the Dertzbaugh reference that spanned the BoNT/A H_C domain, see ¶ 59, lines 4-8; and ¶ 91, lines 1-4. Although not expressly disclosed, because the BoNT/A H_C domain approximately comprises amino acids 872-1269, these fragments most likely correspond to BoNT/A fragments 780-939, 915-1059, 982-1123, 1078-1220 and 1150-1289, see the Dertzbaugh reference, p. 1540, Figure 1. In analyzing which BoNT/A fragment bound to neutralizing anti-BoNT/A antibodies, the Bavari publication states that "only immunization with the 1150-1289 peptide . . . protected mice from BoNT/A challenge." See ¶ 91, lines 18-22. This disclosure indicates that the BoNT/A fragment containing amino acids 785-803 (BoNT/A fragment 780-939) did not provide protective immunity. As discussed above, the inability of a BoNT/A fragment to provide any protective immunity would be interpreted by a person of ordinary skill in the art that antibodies produced by this fragment would not interfere with BoNT/A activity, indicating that such antibodies would not cause immunoresistance to a botulinum toxin therapy in an individual. Thus, like the Dertzbaugh reference, the Bavari publication teaches that amino acids 785-803 from BoNT/A would not work for detecting anti-BoNT/A antibodies that cause immunoresistance to a botulinum toxin therapy because BoNT/A fragment 780-939 did not elicit protective immunity. Thus, a person of ordinary skill in the art would not use a BoNT/A peptide consisting of amino acids 785-803 in a method of predicting or determining immunoresistance to botulinum toxin therapy as presently claimed in Claims 1-16 because, according to the Bavari publication, this BoNT/A peptide would not recognized anti-BoNT/A antibodies that cause immunoresistance. As a BoNT/A peptide consisting of amino acids 785-803 of SEQ ID NO: 1 is an element recited in Claims 1-16, the Bavari publication teaches away for the presently claimed method.

While, the Bavari publication did disclose the use of three 25 amino acid peptides, this disclosure cannot overcome the teaching away of the Bavari publication because none of the fragments contain amino acids 785-803, see Table 4. Furthermore, although the one BoNT/A peptide was from the H_N domain, the use of this peptide was as a negative control,

further indicating that the Bavari publication taught away from using BoNT/A peptides from the H_N domain in a manner as currently claimed by the present application, see, ¶¶ 92-93.

Thus, the Applicants respectfully submit that a *prima facie* case of obviousness cannot be made because the teaching of both the Dertzbaugh reference and the Bavari publication expressly teach away from 1) using 19 or 22 amino acid BoNT/A peptides in a method of determining immunoresistance to botulinum toxin therapy; and 2) using a BoNT/A peptide consists of amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof in a method of determining immunoresistance to botulinum toxin therapy. Therefore, the Applicants respectfully submit that this rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 1-16.

II. Claims 54-61, 63 and 67-73

Claims 54-61, 63 and 67-73 directed, in part, toward a method of predicting or determining immunoresistance to botulinum toxin therapy in an individual where the presence of antibodies immunoreactive with specific BoNT/A peptides indicates immunoresistance to a botulinum toxin therapy. Thus, like Claims 1-16, the method recited in Claims 54-61, 63 and 67-73 use specific BoNT/A peptides to detect the presence of neutralizing anti-BoNT/A antibodies. A BoNT/A peptide recited in each of Claims 54-61, 63 and 67-73 has an amino acid of at most 60 of amino acids and comprises the amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof.

Dertzbaugh and Bavari teach away from the claimed method

According to MPEP § 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The Applicants respectfully submit that it would not be obvious to combine the cited references because the both the Dertzbaugh reference and the Bavari publication teach away from a method of determining immunoresistance to botulinum toxin therapy using a BoNT/A peptide having an amino acid of at most 60 of amino acids and comprising the amino acids 785-803 of SEQ

ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof as presently claimed in Claims 54-61, 63 and 67-73.

As discussed above for Claims 1-16, both the Dertzbaugh reference and Bavari publication teach away from a BoNT/A fragments having a length of at most 60 amino acids and comprising amino acids 785-803 because these references teach 1) BoNT/A peptides having a length of at most 60 amino acids would not work because these fragments would not maintain the tertiary structure required to elicit an immune response; 2) this BoNT/A peptide is located within the H_N domain of BoNT/A; and 3) BoNT/A fragments comprising amino acid 785-803 did not elicit any protective immunity. As such, a person of ordinary skill in the art would interpret this data to mean that antibodies produced by a BoNT/A fragment comprising amino acids 785-803 of SEQ ID NO: 1 would be non-neutralizing anti-BoNT/A antibodies incapable of causing immunoresistance to a botulinum toxin therapy in an individual. Thus, a person of ordinary skill in the art would not use a BoNT/A fragment comprising amino acids 785-803 in a method of predicting or determining immunoresistance to botulinum toxin therapy as presently claimed in Claims 54-61, 63 and 67-73 because, according to both the Dertzbaugh reference and Bavari publication, this BoNT/A fragment would not recognized anti-BoNT/A antibodies that cause immunoresistance.

Thus, the Applicants respectfully submit that a *prima facie* case of obviousness cannot be made because the teaching of both the Dertzbaugh reference and the Bavari publication expressly teach away from a method of determining immunoresistance to botulinum toxin therapy using a BoNT/A peptide having at most 60 amino acids of SEQ ID NO: 1 and comprising amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof. Therefore, the Applicants respectfully submit that this rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 54-61, 63 and 67-73.

III. Claims 93, 94 and 96-101

Claims 93, 94 and 96-101 are directed, in part, toward a BoNT/A peptide having a length of 30 amino acids and comprising one of 12 specific sequences having a length of 19 amino acids: amino acids 491-509, amino acids 519-537 of SEQ ID NO: 1, amino acids 533-551 of

SEQ ID NO: 1, amino acids 547-565 of SEQ ID NO: 1, amino acids 589-607 of SEQ ID NO: 1, amino acids 631-649 of SEQ ID NO: 1, amino acids 673-691 of SEQ ID NO: 1, 715-733 of SEQ ID NO: 1, amino acids 743-761 of SEQ ID NO: 1, amino acids 771-789 of SEQ ID NO: 1, amino acids 785-803 of SEQ ID NO: 1, amino acids 813-831 of SEQ ID NO: 1 and a conservative BoNT/A amino acid sequence variant thereof.

Dertzbaugh and Bavari provide no teaching, suggestion or motivation to combine

According to MPEP § 2143.01, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The Applicants respectfully submit that a *prima facie* obviousness case fails because the Dertzbaugh reference and the Bavari reference do not provide any motivation, suggestion or teaching that would lead a person skilled in the art to specifically make a BoNT/A composition comprising one of the 12 specific sequences as presently claimed in Claims 93, 94 and 96-101.

As discussed above for Claims 1-16, the Dertzbaugh reference teaches away from a BoNT/A peptide of at most 30 amino acids in length because, according to this reference, such BoNT/A peptides would not work because these peptides do not maintain the tertiary structure required to elicit an immune response. Thus, a person of ordinary skill in the art would not make a BoNT/A peptide having a length of at most 30 amino acids as presently claimed in Claims 93, 94 and 96-101 because, according to the Dertzbaugh reference, these BoNT/A peptides would not maintain the tertiary structure required to recognize anti-BoNT/A antibodies. As a BoNT/A peptide having a length of at most 30 amino acids of SEQ ID NO: 1 is an element recited in Claims 93, 94 and 96-101, the Dertzbaugh reference teaches away from the presently claimed method.

The teachings of the Bavari publication cannot make up for the deficient teachings of the Dertzbaugh reference because this patent fails to provide any teaching contrary to the Dertzbaugh reference. As discussed above in Claims 1-16, the Bavari publication also teaches away from the use of BoNT/A peptides having a length of at most 30 amino acids

as presently claimed. The Bavari publication teaches the use of large BoNT/A fragments of approximately 140-160 amino acids to generate antibodies, see ¶ 59, lines 4-8; and ¶ 91, lines 1-4. Only after determining whether such BoNT/A fragments produced neutralizing antibodies were synthetic BoNT/A peptides used to further map antigenic epitopes of these already identified larger fragments, see, e.g., ¶¶ 30-31; Examples 1-3. The Bavari publication found that only BoNT/A fragment 1150-1289 elicited a protective response and disclosed three non-overlapping BoNT/A peptides consisting of amino acids 449-473, 1157-1181 and 1230-1253 that were used to more precisely map the location of the protective epitopes contained in the larger BoNT/A fragments, see ¶ 91, lines 18-22; and Table 4. BoNT/A peptide 449-473 was used as a negative control and BoNT/A peptides 1157-1181 and 1230-1253 were used to further map the protective epitopes present in BoNT/A fragment 1150-1289, see, e.g., ¶ 92; and Table 4. Thus, the Bavari publication teaches the use of small BoNT/A peptides only after larger peptides identified a region of interest.

The Bavari publication does not provide any motivation, suggestion or teaching that would lead a person skilled in the art to specifically make a BoNT/A peptide as presently claimed because this publication teaches that only the BoNT/A fragment consisting of amino acids 1150-1289 elicited a protective immune response. As such, while there may be a motivation to make BoNT/A peptides having a length of no more than 30 amino acids within this region, there would be no such guidance to make BoNT/A peptides outside this region. For example, seven of the amino acid sequences presently claimed comprise amino acids 631-649 of SEQ ID NO: 1, amino acids 673-691 of SEQ ID NO: 1, 715-733 of SEQ ID NO: 1, amino acids 743-761 of SEQ ID NO: 1, amino acids 771-789 of SEQ ID NO: 1, amino acids 785-803 of SEQ ID NO: 1, amino acids 813-831 of SEQ ID NO: 1. The Bavari reference (as well as the Dertzbaugh reference) teaches that antibodies made from BoNT/A fragments comprising these seven amino acid sequences do not elicit a protective immune response. As such, a person skilled in the art would not be motivated to make one of these seven BoNT/A peptide to map protective epitope regions because the larger fragment comprising these seven regions did not provide protective immunity.

Likewise, with respect to the remaining five amino acid sequences presently claimed (amino acids 491-509, amino acids 519-537 of SEQ ID NO: 1, amino acids 533-551 of SEQ ID NO: 1, amino acids 547-565 of SEQ ID NO: 1, amino acids 589-607 of SEQ ID NO: 1), while the

Dertzbaugh reference disclosed potential protective epitopes using BoNT/A fragment 455-661, the subsequent work disclosed in the Bavari publication showed that the BoNT/A fragment 455-661 did not elicit a protective immune response. As such, the Bavari publication did not synthesize smaller BoNT/A peptides for the 455-661 amino acid region. Thus, the Bavari publication does not make up for the teaching of the Dertzbaugh reference, this publication actually contradicts its teaching. This conflicting evidence would hardly motivate a person skilled in the art to make smaller BoNT/A peptides to map protective epitope regions of the BoNT/A fragment of such questionable character.

Thus, the Applicants respectfully submit that the assertion of obviousness is unsupported by the cited references because none of these references provide any explicit or implicit teaching, suggestion or motivation to specifically make a BoNT/A composition comprising one of the 12 specific sequences as presently claimed. As such, it would not have been obvious for a person skilled in the art to modify or combined the BoNT/A fragments disclosed in the Dertzbaugh reference with the Bavari publication, as suggested by the Examiner, in order to arrive at the BoNT/A peptides comprising one of the 12 specific sequences as presently claimed. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) obviousness rejection for Claims 93, 94 and 96-101.

IV. Claims 114-121

Claims 114-121 are directed, in part, toward an immune response inducing composition comprising an adjuvant and a BoNT/A peptide of SEQ ID NO: 1 having a length of at most 60 amino acids and comprising amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof that is capable of stimulating an immune response that produces neutralizing anti-BoNT/A antibody.

Dertzbaugh and Bavari teach away from the claimed method

According to MPEP § 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The Applicants respectfully submit that it would not be obvious to combine the cited references because the both the Dertzbaugh reference and the Bavari publication teach away from an immune

response inducing composition comprising an adjuvant and a BoNT/A peptide of SEQ ID NO: 1 having a length of at most 60 amino acids and comprising amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof that is capable of stimulating an immune response that produces neutralizing anti-BoNT/A antibody as presently claimed in Claims 114-121..

As discussed above for Claims 1-16, both the Dertzbaugh reference and Bavari publication teach away from a BoNT/A fragments having a length of at most 60 amino acids and comprising amino acids 785-803 because these references teach 1) BoNT/A peptides having a length of at most 60 amino acids would not work because these fragments would not maintain the tertiary structure required to elicit an immune response; 2) this BoNT/A peptide is located within the H_N domain of BoNT/A; and 3) BoNT/A fragments comprising amino acid 785-803 did not elicit any protective immunity. As such, a person of ordinary skill in the art would interpret this data to mean that antibodies produced by a BoNT/A fragment comprising amino acids 785-803 of SEQ ID NO: 1 would be non-neutralizing anti-BoNT/A antibodies incapable of causing immunoresistance to a botulinum toxin therapy in an individual. Thus, a person of ordinary skill in the art would not use a BoNT/A peptide comprising amino acids 785-803 for stimulating an immune response in order to produce neutralizing anti-BoNT/A antibodies as presently claimed in Claims 114-121 because, according to both of these cited references, such a BoNT/A peptide produces only non-neutralizing anti-BoNT/A antibodies.

Thus, the Applicants respectfully submit that a *prima facie* case of obviousness cannot be made because the teaching of both the Dertzbaugh reference and the Bavari publication expressly teach away from an immune response inducing composition comprising an adjuvant and a BoNT/A peptide of SEQ ID NO: 1 having a length of at most 60 amino acids and comprising amino acids 785-803 of SEQ ID NO: 1, a conservative variant thereof or an immunoreactive fragment thereof that is capable of stimulating an immune response that produces neutralizing anti-BoNT/A antibody. Therefore, the Applicants respectfully submit that this rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 114-121.

V. Claims 123-133

Claims 123-133 are directed, in part, toward a method of preparing an anti-BoNT/A antibody comprising the step of administering to an animal a composition comprising an adjuvant and a BoNT/A peptide of SEQ ID NO: 1 a having a length of at most 30 amino acids and comprising one of 14 specific sequences having a length of 19 amino acids: amino acids 491-509, amino acids 519-537, amino acids 533-551, amino acids 547-565, amino acids 589-607, amino acids 631-649, amino acids 659-677, amino acids 673-691, 715-733, amino acids 743-761, amino acids 771-789, amino acids 785-803, amino acids 813-831, amino acids 827-845 and an immunogenic BoNT/A amino acid sequence fragment thereof.

Dertzbaugh and Bavari teach away from the claimed method

According to MPEP § 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The Applicants respectfully submit that it would not be obvious to combine the cited references because the both the Dertzbaugh reference and the Bavari publication teach away from a method of preparing anti-BoNT/A antibodies comprising one of the 14 specific sequences as presently claimed in Claims 123-133.

As discussed above in Claims 1-16, the Dertzbaugh reference teaches away from the use of BoNT/A peptides having a length of at most 30 amino acids to prepare anti-BoNT/A antibodies because, according to the teachings of this reference, such fragments would not maintain the tertiary structure required to elicit an immune response.

The Bavari publication does not provide any teaching that is contrary to or makes up for the deficiencies in the Dertzbaugh reference. As discussed above in Claims 1-16, the Bavari publication used the same BoNT/A fragments of approximately 140-160 amino acids disclosed in the Dertzbaugh reference to generate antibodies. The use of the three non-overlapping BoNT/A peptides consisting of amino acids 449-473, 1157-1181 and 1230-1253 were used only to more precisely map the location of the protective epitopes present in the larger BoNT/A fragment 1150-1289, see, e.g., ¶ 59, lines 4-8; and ¶ 91, lines 1-4. It was only after the identification of a larger BoNT/A fragment that produced protective immunity

were these three smaller BoNT/A peptides used to produce anti-BoNT/A antibodies, ¶¶ 93-94.

Thus, the Bavari publication teaches away from a method of preparing an anti-BoNT/A antibody using one of the recited 14 BoNT/A peptides. First, the Bavari publication followed the teaching of the Dertzbaugh in using larger BoNT/A fragments to generate antibodies, see, e.g., ¶ 59, lines 1-4; and ¶ 91, lines 1-4. Second, the use of specific BoNT/A peptides to generate anti-BoNT/A antibodies was determined by whether a larger BoNT/A fragment elicited protective immunity, see, e.g., ¶¶ 30-31; and Examples 1-3. Third, as discussed above for Claims 93, 94 and 96-101, the Bavari publication teaches away from preparing anti-BoNT/A antibodies using one of the 14 presently claimed BoNT/A peptides because this reference discloses that the larger BoNT/A fragments comprising these 14 BoNT/A peptides did not elicit protective immunity, see, e.g., ¶ 91, lines 4-8. As such, a person of ordinary skill in the art following the teaching contained in the Bavari publication, would not make anti-BoNT/A antibodies using one of the presently claimed BoNT/A peptides because this would be contrary to the teaching of the Bavari publication.

Thus, the Applicants respectfully submit that a *prima facie* case of obviousness cannot be made because the teaching of both the Dertzbaugh reference and the Bavari publication expressly teach away from a method of preparing an anti-BoNT/A antibody comprising the step of administering to an animal a composition comprising an adjuvant and a BoNT/A peptide of SEQ ID NO: 1 a having a length of at most 30 amino acids and comprising one of 14 specific sequences having a length of 19 amino acids as presently claimed in Claims 123-133. Therefore, the Applicants respectfully submit that this rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 123-133.

Conclusion

For the reasons stated above, the Applicants respectfully submit that the assertion of obviousness is unsupported by the cited references because the teachings of the cited references 1) teach away from the method of determining immunoresponse to botulinum toxin therapy using BoNT/A peptides as presently claimed in Claims 1-16, 55-61, 63 and

67-73; 2) provide no teaching, suggestion or motivation to a person of ordinary skill in the art to make the BoNT/A peptides as presently claimed in Claims 93-94 and 96-101; 3) teach away from the immune response inducing composition comprising an adjuvant and a BoNT/A peptide as presently claimed in Claims 114-121; and 4) teach away from the method of preparing anti-BoNT/A antibodies as presently claimed in Claims 123-133. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) obviousness rejection for Claims 1-16, 55-61, 63, 67-73, 93, 94, 96-101, 104-112, 123-133.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent. Please use Deposit Account 01-0885 for the payment of any extension of time fees pursuant to 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

/Dean G. Stathakis/

Dean G. Stathakis, Ph.D.
Registration No. 54,465
Agent of Record



ALLERGAN

LEGAL DEPARTMENT

2525 Dupont Drive

Irvine, California 92612-1599

Tel: 714/246-6521

Fax: 714/246-4249